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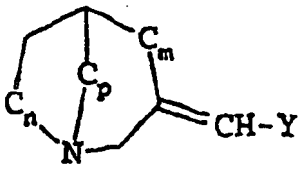
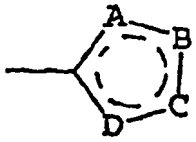
(54) Title: NOVEL SUBSTITUTED AZABICYCLIC COMPOUNDS

(57) Abstract

A compound of formula (I), wherein p is 1 and m is 0 and n is 1 or 2, or p is 1 and m is 1 and n is 1, or p is 2 and m is 0 and n is 1; and wherein Y is formula (a). The present invention relates to therapeutically active heterocyclic compounds (I), to methods for their preparation and to pharmaceutical compositions comprising the compounds. The novel compounds are useful in treating diseases in the central nervous system related to malfunctioning of the nicotinic cholinergic system.



(I)



(a)

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NOVEL SUBSTITUTED AZABICYCLIC COMPOUNDS

Field of the Invention

The present invention relates to heterocyclic compounds which are cholinergic ligands selective for neuronal nicotinic channel receptors, to methods for their preparation, to pharmaceutical compositions comprising them, and to their use in treating cognitive, neurological and mental disorders, which are characterized by decreased nicotinic cholinergic function. The invention also relates to a method of treating Parkinson's disease by modulating the process of dopamine secretion, a method of treating or preventing withdrawal symptoms caused by cessation of chronic or long term use of tobacco products, as well as a method for treating obesity.

Background of the Invention

Nicotinic and muscarinic receptors are the two distinct types of cholinergic receptors named after their selectivity for muscarine and nicotine, respectively. The cholinergic system is the neurotransmitter system that best correlates with memory and cognitive functions. Traditionally, the cholinergic hypothesis for senile dementia of the Alzheimer type (SDAT) has focused on muscarinic acetylcholine receptors (mAChR), and only recently an interest in the role of the nicotinic acetylcholine receptors (nAChR) in SDAT has emerged. This interest was spurred by the relatively recent discovery that nAChR are not only located on the skeletal muscle but also in the brain.

It has been shown that the number of nAChR were decreased in SDAT patients (Nordberg et al., J. Neurosci. Res.Vol. 31, pp. 103-111 (1992); Giacobini, Advances in Experimental Medicine and Biology, Vol. 296, pp.9205-9295, (1993); Schroeder et al., Neurobiol. of Aging, Vol. 12, pp. 259-262, (1991); Whitehouse et al., Neurology, Vol. 38, pp. 720-723, (1988); Flynn and Mash, J. Neurochem., Vol. 47, pp. 8702-8702,

(1993)). Similar deficiencies in choline acetyltransferase activity and acetylcholine synthesis suggest that presynaptic receptors on cholinergic nerve terminals are preferentially lost in SDAT (Nordberg, J. Reprod. Fert. Suppl., Vol 46, pp. 145-154, (1993)). Therefore, it has been assumed that the loss of nAChR may correlate with age related onset of disorders of memory and cognitive functions, and that nicotinic replacement therapy may prove beneficial in SDAT. Indeed nicotine improved attention and memory in healthy humans (Warburton, Prog. Neuro. Psychopharmacol. Biol., Psychiatry, Vol. 16, pp. 181-191,.(1992)) as well as in Alzheimer's disease patients, (Jones et al., Psychopharmacology, Vol. 108, pp. 485-494, (1992); Gitelman and Prohovnik, Neurobiol. of Aging, Vol. 13, pp. 313-318, (1992); Newhouse et al., Psychopharmacology, Vol. 95, pp. 171-175, (1988); Sahakian et al., Br. J. Psychiatry, Vol.154, pp. 9004-904, (1993)). Further the nicotinic antagonist mecamylamine has been shown to cause cognitive impairment in an age related way, (Newhouse et al., Neuropsychopharmacology, Vol 10, pp. 93-107, (1994)).

Parkinson's disease (PD) is a debilitating neurodegenerative disease, presently of unknown etiology, characterized by tremors and muscular rigidity. There is evidence that nicotine may also have beneficial effects in PD. Studies show that smoking may protect against the development of PD, (Ishikawa and Mmiyatake, J. Neurol. Sci., Vol. 117, pp. 28-32, (1993); Godwin-Austen et al., J. Neurol. Neurosurg. Psychiat., Vol. 45, pp. 577-581, (1982); Reavill, in Nicotine psychopharmacology: Molecular, cellular and behavioral aspects, pp. 307-340, Oxford University Press, (1990)), and that chronic nicotine may protect against cell loss in the substantia nigra caused by lesioning (Janson and Moller, Neuroscience, Vol. 57, 931-941, (1993)). Nicotine has also shown beneficial effects in Tourette's syndrome (Sanberg et al., Biomed. Phamacother., Vol. 43, pp. 19-23, (1989)). Alleviation of negative psychotic symptoms, known as the hypofrontality syndrome in schizophrenia, by nicotinic

agonists, have been suggested by data showing that nicotine stimulates dopamine release in the nucleus accumbens more potently than in striatum, (Rowell et al. J. Neurochem., Vol. 49, pp. 1449-1454, (1987); Giorguieff-Chesselet et al., Life Sciences, Vol. 25, pp. 1257-1262, (1979)), by nicotinic reversal of inactivation of prefrontal neurons (Svenson et al., In the Biology of Nicotine dependence., pp. 169-185, New York, (1990)), and by the observation that nicotine will potentiate dopaminergic effects in various behavioral models, (Reavill, in Nicotine psychopharmacology: Molecular, cellular and behavioral aspects, pp. 307-340, Oxford University Press, (1990); Rosecrans et al., Psychopharmacol. Commmun., Vol. 2, pp. 349-356, (1976); Reavill and Stolerman, J. Psychopharmacol., Vol. 1, pp. 264, (1987)).

In recent years there have been several studies on the effects of nicotine and food consumption and associated changes in body weight in rat and human. (Greenberg et al., Addictive behaviours, Vol. 7, pp. 317-331, (1982) and Greenberg et al., Psychopharmacology, Vol. 90, pp. 101-105, (1984)). The appetite effects of nicotine have been suggested to be mediated via modulation of CCK peptides in the paraventricular hypothalamic nucleus (Fuxe et al., Acta Physiologica Scandinavica, Vol. 125, pp. 437-443, (1985)).

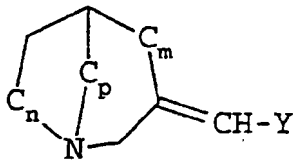
EP 414394 discloses a class of methyleneazabicyclic compounds, substituted with a five membered heterocyclic ring described as cholinergic compounds which enhance acetylcholine function via an action at muscarinic receptors within the central nervous system.

Description of the invention

It is an object of the invention to provide compounds with affinity and selectivity for nicotinic cholinergic receptors, to methods for their preparation, to pharmaceutical compositions containing them, and to their use

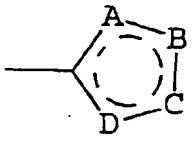
in treating Alzheimer's disease, Parkinson's disease, Tourette's syndrome, ulcerative colitis, obesity, other central nervous system and gastrointestinal disorders, severe pain as well as withdrawal symptoms caused by cessation of chronic or long term use of tobacco products.

The present invention relates to novel substituted azabicyclic compounds of formula I



(I)

wherein p is 1 and m is 0 and n is 1 or 2, or p is 1 and m is 1 and n is 1, or p is 2 and m is 0 and n is 1; and
wherein Y is



wherein -A-B-C-D- is selected from

$=C(R^1)-O-N=C(R^2)-$, $=C(R^1)-S-N=C(R^2)-$, $=C(R^1)-N=C(R^2)-O-$,
$=C(R^1)-C(R^2)=C(R^3)-O-$, $=C(R^1)-C(R^2)=N-O-$, $=C(R^1)-N=C(R^2)-S-$,
$=C(R^1)-C(R^2)=C(R^3)-S-$, $=C(R^1)-C(R^2)=N-S-$, $-C(R^1)=C(R^2)-O-C(R^3)=$,

$-C(R^1)=C(R^2)-S-C(R^3)=$, $-N(R^4)-N=C(R^1)-C(R^2)=$,
$=N-N(R^4)-C(R^1)=C(R^2)-$, $=N-O-C(R^1)=C(R^2)-$, $=N-S-C(R^1)=C(R^2)-$,
$-N(R^4)-C(R^1)=N-C(R^2)=$, $-N=C(R^1)-N(R^4)-C(R^2)=$,
$=C(R^1)-N(R^4)-N=C(R^2)-$, $-N=C(R^1)-O-C(R^2)=$, $-N=C(R^1)-S-C(R^2)=$,
$=N-C(R^1)=C(R^2)-N(R^4)-$, $=N-C(R^1)=C(R^2)-O-$, $=N-C(R^1)=C(R^2)-S-$,
$-N(R^4)-N=N-C(R^1)=$, $=N-N(R^4)-N=C(R^1)-$, $-N=N-N(R^4)-C(R^1)=$,
$-N(R^4)-N=C(R^1)-N=$, $=N-N(R^4)-C(R^1)=N-$, $=N-N=C(R^1)-N(R^4)-$,
$=N-O-N=C(R^1)-$, $=N-N=C(R^1)-O-$, $-N=C(R^1)-O-N=$, $=N-C(R^1)=N-O-$,
$=N-N=C(R^1)-S-$, $=N-S-N=C(R^1)-$, $=N-C(R^1)=N-S-$, $-N=C(R^1)-S-N=$,
$-N(R^4)-N=N-N=$, $=N-N(R^4)-N=N-$; and

R^1, R^2 and R^3 independently are $-NO_2$, -CN, $-NR^5R^6$, $-OR^7$, $-SR^8$, $-COOR^9$, $-SOR^{10}$, $-SO_2R^{11}$, $-SO_3R^{12}$, C_{3-6}-alkyl, C_{4-6}-alkenyl, C_{4-6}-alkynyl, C_{3-6}-cycloalkyl, $-R^{13}-O-R^{14}$ or $-R^{15}-S-R^{16}$, and R^4 is C_{3-6}-alkyl, C_{2-6}-alkenyl, C_{4-6}-alkynyl, C_{4-6}-cycloalkyl, $-R^{17}-O-R^{18}$ or $-R^{19}-S-R^{20}$, wherein R^5 is H, C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl and wherein R^6 is C_{2-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl and wherein R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{14}, R^{16}, R^{18} and R^{20} independently are hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl or C_{3-7}-cycloalkyl and wherein R^{13}, R^{15}, R^{17} and R^{19} independently are C_{1-6}-alkylene, C_{2-6}-alkenylene or C_{2-6}-alkynylene; or a pharmaceutically acceptable salt thereof.

In a preferred embodiment of the invention -A-B-C-D- is selected from

$=C(R^1)-C(R^2)=N-O-$, $=C(R^1)-C(R^2)=N-S-$, $=N-O-C(R^1)=C(R^2)-$,
$=N-S-C(R^1)=C(R^2)-$,

since these compounds have a preferred selectivity for nicotinic receptors as compared to muscarinic receptors.

In an even more preferred embodiment of the invention -A-B-C-D- is selected from

$=C(R^1)-C(R^2)=N-O-$ and $=C(R^1)-C(R^2)=N-S-$.

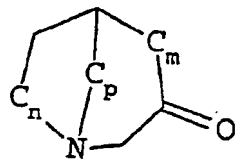
Examples of pharmaceutically acceptable salts include inorganic and organic acid addition salts such as hydrochloride, hydrobromide, sulphate, phosphate, acetate, fumarate, maleate, citrate, lactate, tartrate, oxalate, or similar pharmaceutically-acceptable inorganic or organic acid addition salts, and include the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66, 2 .(1977) which are hereby incorporated by reference.

The compounds of formula I may exist as geometric and optical isomers and all isomers and mixtures thereof are included herein. Isomers may be separated by means of standard methods such as chromatographic techniques or fractional crystallization of suitable salts.

Alkyl, alkenyl and alkynyl as used herein refers to straight or branched alkyl, alkenyl or alkynyl chains.

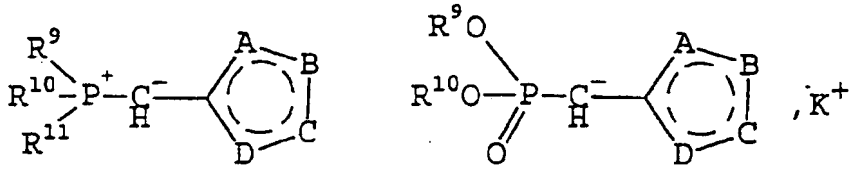
The invention also relates to methods of preparing the above mentioned compounds of formula I. These methods comprise:

a) reacting a compound of formula II



(II)

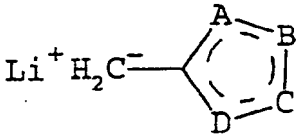
wherein m, n and p have the meanings defined above with a phosphorus ylide of formula III or a phosphonate of formula IV



III IV

wherein R^9, R^{10} and R^{11} independently are C_{1-6}-alkyl, aryl or aralkyl and -A-B-C-D- has the meaning defined above, to give a compound of formula I; or

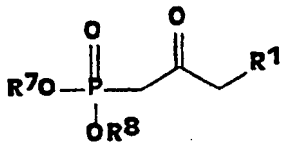
b) reacting a compound of formula II with a compound of formula V



(V)

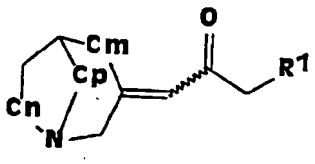
wherein -A-B-C-D- has the meaning defined above, followed by a dehydration to give a compound of formula I; or

c) reacting a compound of formula II with a compound of formula VI



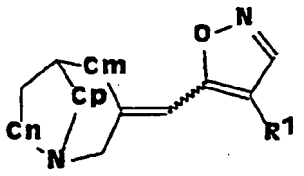
(VI)

wherein R^1, R^7 and R^8 have the meanings defined above, to give a compound of formula VII



(VII)

which is reacted with dimethylformamide dimethylacetale followed by a cyclization with hydroxylamine to give a compound of formula IIX



(IIX)

The pharmacological properties of the compounds of the invention can be illustrated by determining their capability to inhibit the specific binding of ^{3}H-methylcarbamylcholine (^{3}H-MCC) (Abood and Grassi, Biochem. Pharmacol., Vol. 35, pp. 4199-4202, (1986)).

^{3}H-MCC labels the nicotinic receptors in the CNS. The inhibitory effect on ^{3}H-MCC binding reflects the affinity for nicotinic acetylcholine receptors.

Fresh or frozen rat, brain tissue (hippocampus or cortex) was homogenized in assay buffer (50mM Tris-HCl, pH 7.4, 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$) and centrifuged for 10 min. at 40.000 x g. Pellets were subsequently reconstituted in assay buffer and an appropri-

ate amount of tissue sample was mixed in tubes with ^{3}H-methylcarbamylcholine (NEN, NET-951; final concentration 2 nM) and test drug. The tubes were incubated at 0 °C for 60 min. Unbound ligand was separated from bound ligand by vacuum filtration through GF/B filters presoaked in 0.5 % polyethylenimine. Filters were washed three times with 5 ml wash buffer (50mM Tris-HCl, pH 7.4) and transferred to vials. 4 ml scintillation fluid was added and the radioactivity was measured by scintillation counting. Unspecific binding was measured with 10 µM nicotine.

The IC_{50} values of the test compounds were determined by nonlinear regression analyses (GraphPad InPlot).

Furthermore, the pharmacological properties of the compounds of the invention can also be illustrated by determining their capability to inhibit the specific binding of ^{3}H-Oxotremorine-M (^{3}H-Oxo). Birdsdall N.J.M., Hulme E.C., and Burgen A.S.V. (1980). "The Character of Muscarinic Receptors in Different Regions of the Rat Brain". Proc. Roy. Soc. London (Series B) 207,1.

^{3}H-Oxo labels muscarinic receptor in the CNS (with a preference for agonist domains of the receptors). Three different sites are labelled by ^{3}H-Oxo. These sites have affinity of 1.8, 20 and 3000 nM, respectively. Using the present experimental conditions only the high and medium affinity sites are determined.

The inhibitory effects of compounds on ^{3}H-Oxo binding reflects the affinity for muscarinic acetylcholine receptors.

All preparations are performed at 0-4°C unless otherwise indicated. Fresh cortex (0.1-1 g) from male Wistar rats (150-250 g) is homogenized for 5-10 s in 10 ml 20 mM Hepes pH: 7.4, with an Ultra-Turrax homogenizer. The homogenizer is rinsed with 10 ml of buffer and the combined sus-

pension centrifuged for 15 min. at 40,000 x g. The pellet is washed three times with buffer. In each step the pellet is homogenized as before in 2 x 10 ml of buffer and centrifuged for 10 min. at 40,000 x g.

The final pellet is homogenized in 20 mM Hepes pH: 7.4 (100 ml per g of original tissue) and used for binding assay. Aliquots of 0.5 ml is added 25 ul of test solution and 25 ul of ^{3}H-Oxotremorine (1.0 nM, final concentration) mixed and incubated for 30 min. at 25°C. Non-specific binding is determined in triplicate using arecoline (1 ug/ml, final concentration) as the test substance. After incubation samples are added 5 ml of ice-cold buffer and poured directly onto Whatman GF/C glass fiber filters under suction and immediately washed 2 times with 5 ml of ice-cold buffer. The amount of radioactivity on the filters are determined by conventional liquid scintillation counting. Specific binding is total binding minus non specific binding.

Test substances are dissolved in 10 ml water (if necessary heated on a steam-bath for less than 5 min.) at a concentration of 2.2 mg/ml. 25-75% inhibition of specific binding must be obtained before calculation of IC_{50}. The test value will be given as IC_{50} (the concentration (nM) of the test substance which inhibits the specific binding of ^{3}H-Oxo by 50%).

IC_{50} = (applied test substance concentration) $x(C_x/C_o-C_x)$nM

where C_o is specific binding in control assays and C_x is the specific binding in the test assay. (The calculations assume normal mass-action kinetics).

Table I illustrates the affinity of the compounds of the present invention for nicotinic and muscarinic receptors as determined by ^{3}H-MCC and ^{3}H-Oxo binding to rat cortical receptors. The compounds, however, show selective affinity for nicotinic receptors as compared to muscarinic

receptors, i.e OXO/MCC > 1.

Table 1

Compound	^{3}H-MCC IC_{50} nM	^{3}H-Oxo IC_{50} nM	Oxo/MCC Ratio
1	140	1400	10
3	470	34000	72
7	580	10000	17

The compounds of the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.05 to about 100 mg, preferably from about 0.1 to about 100 mg, per day may be used. A most preferable dosage is about 10 mg to about 70 mg per day. In choosing a regimen for patients suffering from diseases in the central nervous system caused by malfunctioning of the nicotinic cholinergic system it may frequently be necessary to begin with a dosage of from about 30 to about 70 mg per day and when the condition is under control to reduce the dosage as low as from about 1 to about 10 mg per day. The exact dosage will depend upon the mode of administration, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral or parenteral e.g. rectal, transdermal, subcutaneous, intravenous, intraurethral, intramuscular, topical, intranasal, ophthalmic solution or an ointment, the oral route being preferred.

Typical compositions include a compound of formula I or a pharmaceuti-

cally acceptable acid addition salt thereof, associated with a pharmaceutically acceptable carrier. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone.

The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or coloring substances and the like, which do not deleteriously react with the active compounds.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

Generally, the compounds are dispensed in unit form comprising from about 1 to about 100 mg in a pharmaceutically acceptable carrier per unit

dosage.

A typical tablet, appropriate for use in this method, may be prepared by conventional tabletting techniques and contains:

Active compound	5.0 mg
Lactosum	67.8 mg Ph.Eur.
Avicel®	31.4 mg
Amberlite®	1.0 mg
Magnesii stearas	0.25 mg Ph. Eur.

The invention will now be described in further detail with reference to the following examples:

EXAMPLE 1

3-Hydroxy-3-(3-methoxymethyl-5-isoxazolyl)methyl-1-azabicyclo[2.2.2]-octane

A solution of 3-methoxymethyl-5-methylisoxazol (2.52 g, 20 mmol) in dry tetrahydrofuran (5 ml) was added to a solution of LDA (22.5 mmol) in dry tetrahydrofuran (30 ml) cooled to -78°C. The reaction mixture was stirred at -78°C for 15 min. A solution of quinuclidinone (2.3 g, 20 mmol) dissolved in dry tetrahydrofuran (10 ml) was added. The reaction mixture was stirred for 0.5 h at -78°C, then quenched with water (100 ml) and acidified with concentrated hydrochloric acid. The water phase was extracted with ether (2 x 50 ml), then basified with solid potassium carbonate and extracted with methylene chloride (4 x 100 ml). The methylene chloride phases were collected and dried over magnesium sulphate. After evaporation of the solvent the title compound was isolated in 1.4 g yield.

(Z)-3-(3-Methoxymethylisoxazol-5-yl)methylene-1-azabicyclo[2.2.2]octane oxalate and (E)-3-(3-methyoxymethylisoxazol-5-yl)methylene-1-azabicyclo[2.2.2]octane oxalate

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To a solution of 3-hydroxy-3-(3-methyl-5-isoxazolyl)methyl-1-azabicyclo-[2.2.2]octane (1.4 g) in methylene chloride (30 ml) was added triethylamine (2.2 g, 25 mmol). The reaction mixture was cooled to 0°C, and thionyl chloride (2.0 g, 17 mmol) in methylene chloride (10 ml) was carefully added. The reaction mixture was stirred at 0°C for 1 h and then poured on ice. The phases were separated and the water phase made alkaline with solid potassium carbonate. The water phase was extracted with ether (4 x 100 ml). The ether phases were dried over magnesium sulphate and evaporated giving a crude mixture of Z and E isomers. The title compounds were separated by column chromatography on silica (eluent: ethyl acetate/methanol/ammonium hydroxide: 2/1/2%). The first fractions contained the Z isomer which after crystallization with oxalic acid gave (Z)-3-(3-methoxymethylisoxazol-5-yl)methylene-1-azabicyclo-[2.2.2]octane oxalate in 25% yield. M.p. 139-140°C. (Compound 1). The next fractions contained the E isomer which after crystallization with oxalic acid gave (E)-3-(3-methoxymethylisoxazol-5-yl)methylene-1-azabicyclo[2.2.2]octane oxalate in 28% yield. M.p. 162-163°C. (Compound 2).

EXAMPLE 2

The following compounds were prepared in exactly the same manner as described in example 1:

(Z)-6-(3-isopropyl-5-isoxazolyl)methylene-1-azabicyclo[2.2.2]octane oxalate, starting from 1-azabicyclo[2.2.2]octan-3-one and 3-isopropyl-5-methylisoxazole. M.p. 145-147°C. (Compound 3).

(E)-6-(3-isopropyl-5-isoxazolyl)methylene-1-azabicyclo[2.2.2]octane oxalate, starting from 1-azabicyclo[2.2.2]octan-3-one and 3-isopropyl-5-methylisoxazole. M.p. 130-133°C. (Compound 4).

EXAMPLE 3

(Z)-3-(3-propylisoxazol-5-yl)methylene-1-azabicyclo[2.2.2]octane oxalate and (E)-3-(3-propylisoxazol-5-yl)methylene-1-azabicyclo[2.2.2]octane oxalate

To a solution of 3-propyl-5-methylisoxazol (1.31 g, 10 mmol) in dry tetrahydrofuran (30 ml) cooled to -78°C was added n-BuLi (2.5 M in hexane, 12.5 mmol). The reaction mixture was stirred at -78°C for 20 min. A solution of quinuclidinone (0.92 g, 8.0 mmol) dissolved in dry tetrahydrofuran (5 ml) was added. The reaction mixture was stirred for 0.5 h at -78°C. Triethylamine (2.25 g, 25 mmol) and thionyl chloride (4.0 g, 34 mmol) was added and the reaction mixture slowly heated to room temperature. The reaction mixture was quenched with water (100 ml) and acidified with concentrated hydrochloric acid. The water phase was extracted with ether (2 x 50 ml), then made alkaline with solid potassium carbonate and extracted with ether (4 x 100 ml). The ether phases were dried over magnesium sulphate and evaporated giving a crude mixture of Z and E isomers. The title compounds were separated by column chro-

matography on silica (eluent: ethyl acetate/methanol/ammonium hydroxide: 2/1/2%). The first fractions contained the Z isomer which after crystallization with oxalic acid gave (Z)-3-(3-propylisoxazol-5-yl)methylene-1-azabicyclo[2.2.2]octane oxalate in 7% yield. M.p. 106-108°C. (Compound 5).

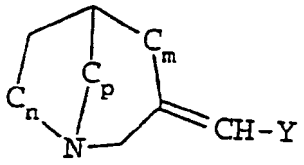
The next fractions contained the E isomer which after crystallization with oxalic acid gave (E)-3-(3-propylisoxazol-5-yl)methylene-1-azabicyclo-[2.2.2]octane oxalate in 22% yield. M.p. 113-115°C. (Compound 6).

In exactly the same manner the following compound was made:

3-(3-propylisoxazol-5-yl)methylene -1-azabicyclo[2.2.1]heptane oxalate from 1-azabicyclo[2.2.1]heptan-3-one and 3-propyl-5-methylisoxazole. M.p. 78-80°C. (Compound 7).

CLAIMS

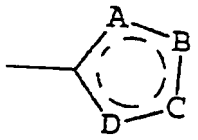
1. A compound of formula I



(I)

wherein p is 1 and m is 0 and n is 1 or 2, or p is 1 and m is 1 and n is 1, or p is 2 and m is 0 and n is 1; and

wherein Y is



wherein -A-B-C-D- is selected from

$=C(R^1)-O-N=C(R^2)-$, $=C(R^1)-S-N=C(R^2)-$, $=C(R^1)-N=C(R^2)-O-$,
$=C(R^1)-C(R^2)=C(R^3)-O-$, $=C(R^1)-C(R^2)=N-O-$, $=C(R^1)-N=C(R^2)-S-$,
$=C(R^1)-C(R^2)=C(R^3)-S-$, $=C(R^1)-C(R^2)=N-S-$, $-C(R^1)=C(R^2)-O-C(R^3)=$,
$-C(R^1)=C(R^2)-S-C(R^3)=$, $-N(R^4)-N=C(R^1)-C(R^2)=$,
$=N-N(R^4)-C(R^1)=C(R^2)-$, $=N-O-C(R^1)=C(R^2)-$, $=N-S-C(R^1)=C(R^2)-$,
$-N(R^4)-C(R^1)=N-C(R^2)=$, $-N=C(R^1)-N(R^4)-C(R^2)=$,
$=C(R^1)-N(R^4)-N=C(R^2)-$, $-N=C(R^1)-O-C(R^2)=$, $-N=C(R^1)-S-C(R^2)=$,
$=N-C(R^1)=C(R^2)-N(R^4)-$, $=N-C(R^1)=C(R^2)-O-$, $=N-C(R^1)=C(R^2)-S-$,
$-N(R^4)-N=N-C(R^1)=$, $=N-N(R^4)-N=C(R^1)-$, $-N=N-N(R^4)-C(R^1)=$,

$-N(R^4)-N=C(R^1)-N=$, $=N-N(R^4)-C(R^1)=N-$, $=N-N=C(R^1)-N(R^4)-$, $=N-O-N=C(R^1)-$, $=N-N=C(R^1)-O-$, $-N=C(R^1)-O-N=$, $=N-C(R^1)=N-O-$, $=N-N=C(R^1)-S-$, $=N-S-N=C(R^1)-$, $=N-C(R^1)=N-S-$, $-N=C(R^1)-S-N=$, $-N(R^4)-N=N-N=$ or $=N-N(R^4)-N=N-$; and

R^1, R^2 and R^3 independently are $-NO_2$, -CN, $-NR^5R^6$, $-OR^7$, $-SR^8$, $-COOR^9$, $-SOR^{10}$, $-SO_2R^{11}$, $-SO_3R^{12}$, C_{3-6}-alkyl, C_{4-6}-alkenyl, C_{4-6}-alkynyl, C_{3-6}-cycloalkyl, $-R^{13}-O-R^{14}$ or $-R^{15}-S-R^{16}$, and R^4 is C_{3-6}-alkyl, C_{2-6}-alkenyl, C_{4-6}-alkynyl, C_{4-6}-cycloalkyl, $-R^{17}-O-R^{18}$ or $-R^{19}-S-R^{20}$, wherein R^5 is H, C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl and wherein R^6 is C_{2-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl and wherein R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{14}, R^{16}, R^{18} and R^{20} independently are hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl or C_{3-7}-cycloalkyl and wherein R^{13}, R^{15}, R^{17} and R^{19} independently are C_{1-6}-alkylene, C_{2-6}-alkenylene or C_{2-6}-alkynylene; or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein -A-B-C-D- is selected from

$=C(R^1)-C(R^2)=N-O-$, $=C(R^1)-C(R^2)=N-S-$, $=N-O-C(R^1)=C(R^2)-$, $=N-S-C(R^1)=C(R^2)-$,

preferably $=C(R^1)-C(R^2)=N-O-$ and $=C(R^1)-C(R^2)=N-S-$,

wherein R^1 and R^2 have the meanings defined above.

3. A compound according to claim 1, wherein the compound is selected from the following:

(Z)-3-(3-Methoxymethylisoxazol-5-yl)methylene-1-azabicyclo[2.2.2]-octane,

(E)-3-(3-Methoxymethylisoxazol-5-yl)methylene-1-azabicyclo[2.2.2]-octane,

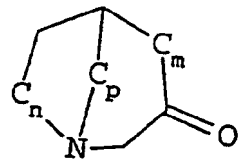
(Z)-6-(3-Isopropyl-5-isoxazolyl)methylene-1-azabicyclo[2.2.2]octane,

(E)-6-(3-Isopropyl-5-isoxazolyl)methylene-1-azabicyclo[2.2.2]octane,

(Z)-3-(3-Propylisoxazol-5-yl)methylene-1-azabicyclo[2.2.2]octane,
(E)-3-(3-Propylisoxazol-5-yl)methylene-1-azabicyclo[2.2.2]octane,
3-(3-Propylisoxazol-5-yl)methylene-1-azabicyclo[2.2.1]heptane; or
a pharmaceutically acceptable salt thereof.

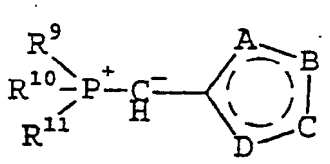
4. A method of preparing a compound according to any of the preceeding claims, CHARACTERIZED IN

a) reacting a compound of formula II

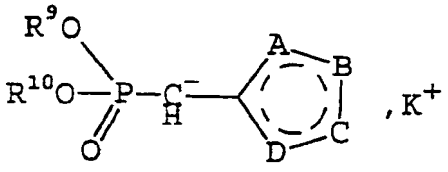


(II)

wherein m, n and p have the meanings defined above with a phosphorus ylide of formula III or a phosphonate of formula IV



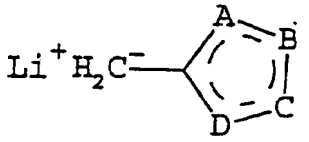
III



IV

wherein R^9, R^{10} and R^{11} independently are C_{1-6}-alkyl, aryl or aralkyl and -A-B-C-D- has the meaning defined above, to give a compound of formula I; or

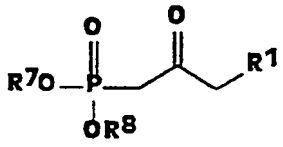
b) reacting a compound of formula II with a compound of formula V



(V)

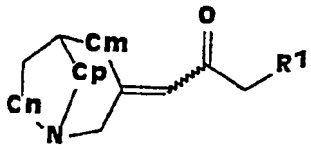
wherein -A-B-C-D- has the meaning defined above, followed by a dehydration to give a compound of formula I; or

c) reacting a compound of formula II with a compound of formula VI



(VI)

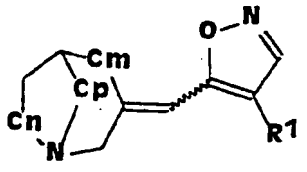
wherein R^1, R^7 and R^8 have the meanings defined above, to give a compound of formula VII



(VII)

wherein m, n, p and R^1 have the meanings defined above, which is reacted with dimethylformamide dimethylacetale followed by a cycliza-

tion with hydroxylamine to give a compound of formula IIX



(IIX)

wherein m, n, p and R^1 have the meanings defined above.

5. A pharmaceutical composition comprising as active component a compound according to any of claims claim 1 to 3 together with a pharmaceutically acceptable carrier or diluent.

6. The pharmaceutical composition according to claim 5 in the form of an oral dosage unit or parenteral dosage unit.

7. The pharmaceutical composition according to claim 6, wherein said dosage unit comprises from about 1 to about 100 mg of the compound according any of claims 1 to 3.

8. A compound according to any of claims 1 to 3 for treating a central nervous system ailment related to malfunctioning of the nicotinic cholinergic system.

9. A compound according to any of claims 1 to 3 for treating Alzheimer's disease, Parkinson's disease, Tourette's syndrome, ulcerative colitis, obesity, gastrointestinal disorders or severe pain, preferably obesity, or for treating or preventing withdrawal symptoms caused by cessation of chronic or long term use of tobacco products, preferably obesity.

10. The use of a compound according to any of claims 1 to 3 for the preparation of a medicament for treatment of a disease in the central nervous system related to malfunctioning of the nicotinic cholinergic system.

11. The use of a compound according to any of claims 1 to 3 for the preparation of a medicament for treatment of Alzheimer's disease, Parkinson's disease, Tourette's syndrome, ulcerative colitis, obesity, gastrointestinal disorders or severe pain, preferably obesity, or for treating or preventing withdrawal symptoms caused by cessation of chronic or long term use of tobacco products.

12. A method of treating a central nervous system ailment related to malfunctioning of the nicotinic cholinergic system in a subject in need of such treatment comprising administering to said subject an effective amount of a compound according to any of claims 1 to 3.

13. A method of treating Alzheimer's disease, Parkinson's disease, Tourette's syndrome, ulcerative colitis, obesity, gastrointestinal disorders or severe pain, preferably obesity, in a subject in need of such treatment comprising administering to said subject an effective amount of a compound according to any of claims 1 to 3.

14. A method of treating or preventing withdrawal symptoms caused by cessation of chronic or long term use of tobacco products comprising administering to a subject in need thereof an effective amount of a compound according to any of claims 1 to 3.

Our Ref: 4412-WO,LaKe

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 96/00294

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 453/02, C07D 487/08, A61K 31/435
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0414394 A2 (BEECHAM GROUP P.L.C.), 27 February 1991 (27.02.91) --	1-11
X	Chemical Abstracts, Volume 86, No 21, 23 May 1977 (23.05.77), (Columbus, Ohio, USA), Mikhlina, E. E. et al, "Synthesis and pharmacological study of quinuclidine analogs of sulpiride and bithiodine", page 456, THE ABSTRACT No 155489r, Khim. Farm. Zh. 1976, 10 (11), 56-60 --	1,4-9
A	EP 0363085 A2 (BEECHAM GROUP PLC), 11 April 1990 (11.04.90) --	1-11

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"B" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 Sept 1996	18 -10- 1996
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK96/00294

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 12-14
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

05/09/96

International application No.
PCT/DK 96/00294

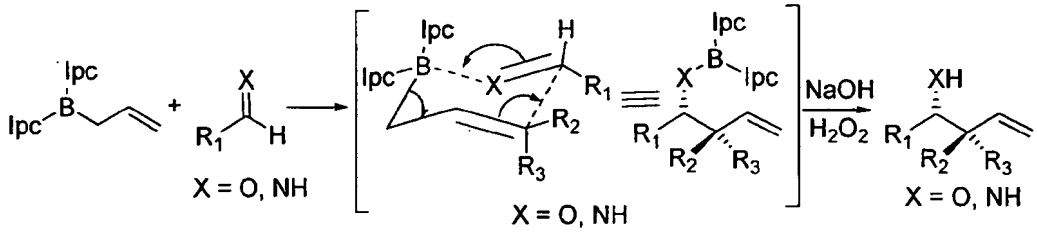
Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A2- 0414394	27/02/91	AT-T- 124697	15/07/95
		AU-B- 629668	08/10/92
		AU-A- 6013090	07/02/91
		DE-D,T- 69020661	11/01/96
		JP-A- 3178976	02/08/91
		US-A- 5470859	28/11/95
EP-A2- 0363085	11/04/90	AU-A- 4242689	26/04/90
		CA-A- 2000042	03/04/90
		JP-A- 2129186	17/05/90
		PT-B- 91872	31/05/95
		US-A- 5091397	25/02/92

STABLE BORANE REAGENTS AND METHODS FOR THEIR USE

Background of the Invention

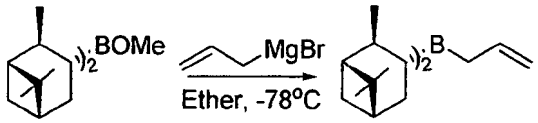
Allylation is one of the extremely important C-C bond forming reactions. Accordingly several "allyl" metal species have been extensively employed in the reaction with functional groups such as carbonyl (C=O) and imine (C=N), leading to the formation of the corresponding homoallylic alcohols or amines respectively. Among the several metals employed for allylation, allylboranes are highly unique and proceed with high stereoselectivity. The diastereoselectivity arises via a rigid six-membered chair like transition state due to the similarities in size of boron and carbon.

There have been significant advances made in the development of enantioselective versions of allylboration utilizing chiral allylboranes derived from α-pinene, tartarate, camphor etc. Of the several chiral auxiliaries employed, α-pinene is of special importance as the corresponding allylboranes result in very high enantiomeric excesses (ee) for a wide variety of aldehydes and imines (Scheme 1). See Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092; Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293; Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919; Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 1535; Ramachandran, P. V.,et al., *Org. Biomol. Chem.* **2005**, *3*, 3812 ; Ramachandran, P. V., et al., *J. Org. Chem.* **2004**, *69*, 6294 ; and Ramachandran, P. V., et al., *J. Org. Chem.* **2002**, *67*, 7547.



Scheme 1: Reaction of allylboranes with carbonyls and imines
Ipc = isopinocampheylborane

The reaction with α-pinene derived boranes is reagent controlled, and the ee of the product obtained depends on the antipode of α-pinene used, regardless of the chirality in the substrate. One such α-pinene reagent is B-*a*llyldiisopino-campheylborane, which provides exceptional enantioselectivity for aldehydes and imines at low temperatures. Unfortunately, B-allyldiisopinocampheylborane is not commercially available, due to its perceived instability. Thus, it is typically generated *in situ* or freshly prepared before use as illustrated in Scheme 2.



Scheme 2: Preparation of $Ipc_2BAllyl$ Reagent

The preparation is tedious and involves the reaction of B-methoxydiisopino-campheylborane with allylmagnesium bromide in ether at 0 °C using Brown's procedure (^{11}B NMR shows a peak at ~ 78 PPM). The reaction generates a large amount of solid methoxymagnesium bromide that needs to be filtered under inert atmosphere, followed by repeated washings with pentane to precipitate the excess Grignard reagent. The reagent thus obtained is typically used for allylboration reactions as a 1-2M solution in pentane at low temperatures (-78 °C to -100°C).

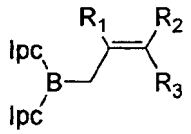
In view of the versatility of this reagent and its enormous potential for application in pharmaceutical industry, there is a need for a stabilized form of B-*a*llyldiisopinocampheylborane that can be stored and sold commercially. There is also a need for improved methods for using the reagent that require less stringent handling requirements.

Summary of the Invention

The invention provides stable forms of B-allyldiisopinocampheylborane that can be stored, shipped, and used on commercial scale. The invention also provides methods for performing allylboration at increased temperatures and in the presence of water. Such methods reduce the need for low temperatures and inert

atmospheres, making the reagent more attractive for use on a commercial scale.

Accordingly in one embodiment, the invention provides a method comprising storing a borane of formula (I):



(I)

wherein R_1, R_2, and R_3 are each independently selected from H, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, aryl, and aryl(C_1-C_6)alkyl; and each Ipc is isopinocampheyl; under conditions such that less than 10% of the borane by weight decomposes after three days.

In another embodiment the invention provides a method comprising treating a compound comprising a carbonyl group or an imine group with B-allyldiisopinocampheylborane that is at least 3 days old.

In another embodiment the invention provides a composition comprising dioxane and B-allyldiisopinocampheylborane.

In another embodiment the invention provides a kit comprising 1) packaging material, and 2) B-allyldiisopinocampheylborane that is at least 3 days old.

In another embodiment the invention provides a method comprising reducing an organic compound with a borane in an aqueous solvent.

In another embodiment the invention provides a method comprising reducing an organic compound with a borane at a temperature of greater than or equal to -5 °C.

Detailed Description

Applicant has determined that borane reagents such as B-allyldiisopino-campheylborane can be stored for months without any appreciable decomposition Additionally, allylboration of aldehydes was carried out with this reagent at ice-salt temperatures instead of -78 °C to -100 °C with only a slight decrease in the enantioselectivity. Remarkably, the reaction can be performed in water at high

temperatures making this procedure environmentally benign and industrially attractive.

The following definitions are used, unless otherwise described: halo is fluoro, chloro, bromo, or iodo. Alkyl, alkoxy, etc. denote both straight and branched groups; but reference to an individual radical such as propyl embraces only the straight chain radical, a branched chain isomer such as isopropyl being specifically referred to. Aryl denotes a phenyl radical or an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic.

The term (C_5-C_{12}) hydrocarbon includes both straight and branched hydrocarbons having from five to twelve carbon atoms as well as mixtures thereof (e.g. pentanes, hexanes, heptanes, octanes, nonanes, decanes, etc.)

The term (C_4-C_{10}) ether includes straight and branched hydrocarbon ethers and aryl ethers having a total of four to ten carbon atoms, and mixtures thereof (e.g. diethylether, diisopropylether, dioxane, phenylmethylether, etc.).

The term halogenated (C_1-C_{10}) hydrocarbon includes both straight and branched hydrocarbons having from five to twelve carbon atoms that are substituted with one or more halo atoms, and mixtures thereof (e.g. dichloromethane, chloroform, trichloromethane, etc.).

Specific values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

Specifically, (C_1-C_6)alkyl can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, pentyl, 3-pentyl, or hexyl; (C_1-C_6)alkoxy can be methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, sec-butoxy, pentoxy, 3-pentoxy, or hexyloxy; and aryl can be phenyl, indenyl, or naphthyl.

A) Stability Studies

The B-allyldiisopinocampheylborane reagent was prepared on a 200 mmol scale. Aliquots of the reagent were taken in 20mL volumetric flasks fitted with a stop cock and standard solutions (1M and 2M) were prepared in various solvents such as pentane, ether, CH_2Cl_2, and 1,4-dioxane (mp 12°C), cyclohexane (mp 7°C), cyclooctane (mp 12°C) and benzene (mp 6°C). Initially, 1M and 2M solutions were refrigerated at 4 °C after determining the purity based on ^{11}B NMR.

The stability of the reagent was evaluated periodically after every one month via ^{11}B NMR. No appreciable decomposition was observed after 4 months in solvents such as dioxane, benzene, and pentane. However, about 10-20 % decomposition was observed in some other solvents tested (e.g. cyclohexane, cyclooctane, dichloromethane, and diethyl ether). Low melting solvents like dioxane and benzene at 4 °C are postulated to impart reagent stabilization due to restricted movement. The non-polar nature of the pentane solutions may assist in long term stabilization of the reagent.

In one embodiment the invention provides a method comprising storing B-allyldiisopinocampheylborane for 10, 30, or 60 days or more. In another embodiment, the B-allyldiisopinocampheylborane is stored at or below about 10 °C. In another embodiment, the B-allyldiisopinocampheylborane is stored at or below about 0 °C. In another embodiment, the B-allyldiisopinocampheylborane is stored at or below about -10 °C. In another embodiment, the invention further provides selling the B-allyldiisopinocampheylborane that has been stored.

In another embodiment, the invention provides a composition comprising dioxane and B-allyldiisopinocampheylborane at a concentration of from about 0.05M to about 5M. In another embodiment, the B-allyldiisopinocampheylborane is present at a concentration of from about 0.5M to about 3M. In another embodiment, the composition is a solid. The compositions of the invention can conveniently be stored at a temperature of from about -78 °C to about 25 °C. In one embodiment,

the compositions of the invention can be stored at a temperature of from about -78 °C to about 25 °C. In another embodiment, the compositions of the invention can be stored at a temperature of from about -78 °C to about 0 °C.

In another embodiment, the invention provides a method for storing B-allyldiisopinocampheylborane comprising combining B-allyldiisopinocampheylborane and a solvent (e.g. dioxane, pentane, or a mixture thereof) to provide a composition, and storing the composition under conditions such that the concentration of B-allyldiisopinocampheylborane in the composition varies by less than about 10% by weight after three days. In another embodiment, the concentration of B-allyldiisopinocampheylborane in the composition varies by less than about 10% by weight after ten days. In another embodiment, the concentration of B-allyldiisopinocampheylborane in the composition varies by less than about 10% by weight after thirty days. In another embodiment, the concentration of B-allyldiisopinocampheylborane in the composition varies by less than about 5% by weight after three days. In another embodiment, the concentration of B-allyldiisopinocampheylborane in the composition varies by less than about 5% by weight after ten days. In another embodiment, the concentration of B-allyldiisopinocampheylborane in the composition varies by less than about 5% by weight after thirty days. In another embodiment, the concentration of B-allyldiisopinocampheylborane in the composition varies by less than about 1% by weight after three days. In another embodiment, the concentration of B-allyldiisopinocampheylborane in the composition varies by less than about 1% by weight after ten days. In another embodiment, the concentration of B-allyldiisopinocampheylborane in the composition varies by less than about 1% by weight after thirty days.

Typically, the compositions can be stored in an inert environment, e.g. under an inert gas such as argon or nitrogen, and/or in an air-tight vial or air-tight ampoule.

In another embodiment, the invention provides a kit comprising 1) packaging material, and 2) a solution comprising B-allyldiisopinocampheylborane that is at

least 3 days old. In another embodiment, the B-allyldiisopinocampheylborane in the kit is at least 10 days old. In another embodiment, the B-allyldiisopinocampheylborane that is in the kit is at least 30 days old.

B) High Temperature Allylboration

High temperature allylboration was performed using $Ipc_2Ballyl$ in pentane, dioxane and benzene on four different aldehydes (benzaldehyde, o-bromobenzaldehyde, propionaldehyde and isobutyraldehyde). Before the addition of the aldehyde, the standard $IPC_2BAllyl$ reagents were diluted with 50 % of pentane. Aldehydes were added at -15 °C, the reactions were stirred at that temperature for 2 minutes, and oxidized under standard $NaOH-H_2O_2$ conditions. Work-up followed by purification afforded the corresponding homoallylic alcohols in good yield. The enantiomeric excesses were checked by comparing the specific rotation values with literature values and cross checked by chiral HPLC analysis using Chiralcel OD-H column with isopropanol-hexanes as eluting agent. Additionally, allylation of acetophenone provided 4-7 % enantiomeric excess of the corresponding homoallylic alcohol at -15 °C, which was identical to the value reported in the literature when the allylation was performed at -78 °C.

In another embodiment, the invention provides a method comprising treating an organic compound with a borane at a temperature of greater than or equal to -5 °C. In another embodiment, the organic compound is treated with a borane at a temperature of greater than or equal to 0 °C. In another embodiment, the organic compound is treated with a borane at a temperature of less than or equal to about 10 °C. In another embodiment, the organic compound comprises a carbonyl or an imine. In another embodiment, the borane is (β)-allyldiisopinocampheylborane. In another embodiment, the compound is allylated with an ee of at least about 80%. In another embodiment, the compound is allylated with an ee of at least about 90%. In another embodiment, the compound is allylated with an ee of at least about 95%.

C) Allylboration of Aldehydes with $IPC_2Ballyl$ in Water

Organic solvents are used extensively in the chemical industry, and their release into the environment has been a matter of great concern. A number of regulations are in place to govern solvents production, use, or disposal due to the wide range of hazards that are associated with these volatile organic compounds. Today, there is much emphasis on reduction of organic solvent usage and on using green chemistry.

Unexpectedly, exceptionally facile asymmetric allylboration of aldehydes with $IPC_2Ballyl$ was carried out in water at high temperatures. It is known that $IPC_2Ballyl$ is quenched in water. However, it has now been determined that $IPC_2Ballyl$ reacts with aldehydes faster than with water.

Thus, in another embodiment, the invention provides a method comprising treating an organic compound with a borane in an aqueous solvent. In another embodiment, the organic compound comprises a carbonyl or an imine. In another embodiment, the borane is B-allyldiisopinocampheylborane. In another embodiment, the aqueous solvent comprises at least about 5% water by weight. In another embodiment, the aqueous solvent comprises at least about 10% water by weight. In another embodiment, the aqueous solvent comprises at least about 50% water by weight. In another embodiment, the aqueous solvent comprises at least about 75% water by weight. In another embodiment, the aqueous solvent is water.

In another embodiment, the invention provides a method comprising treating an organic compound with a borane under an atmosphere that comprises water. In another embodiment, the organic compound comprises a carbonyl or an imine. In another embodiment, the borane is B-allyldiisopinocampheylborane. In another embodiment, the atmosphere comprises at least about 1% water by weight. In another embodiment, the atmosphere comprises at least about 10% water by weight. In another embodiment, the atmosphere comprises at least about 20% water by weight.

The invention will now be illustrated by the following non-limiting Examples.

Example 1. **Allylboration with B-allyldiisopinocampheylborane at high temperature**

Aldehyde (5.0 mmol) was added to a stirred solution of (+)-B-allyldiisopinocampheylborane ($Ipc_2BAllyll$) (7.0 mL, 1M solution) at -15 °C and maintained at that temperature for 2 minutes. The reaction was followed by ^{11}B NMR spectroscopy (δ 56). Upon completion, the mixture was oxidized with 3.0 mL of 3.0 M NaOH and 3.0 mL of 30% H_2O_2, stirred for four hours at room temperature (about 22 ± 3 °C) and extracted with Et_2O. The pure homoallylic alcohol was obtained upon silica gel column chromatography.

Allylboration of aldehydes with standard $IPC_2BAllyl$ reagents

#	Aldehyde	$Ipc_2BAllyl$ in Pentane (% ee)	$Ipc_2BAllyl$ in Dioxane (% ee)
1	C_6H_5CHO	94	92
2	*o*-BrC_6H_4CHO	92	90
3	C_2H_5CHO	92	90
4	$(CH_3)_2CHCHO$	90	89
5	$C_6H_5COCH_3$	7	4

Example 2 **Allylboration with B-allyldiisopinocampheylborane in water as solvent**

(+)-B-allyldiisopinocampheylborane ($Ipc_2BAllyl$) (7.0 mL, 1M solution) was added to a stirred solution of aldehyde (5.0 mmol in 10 mL water) at 5 °C and maintained at that temperature for 2 minutes. The mixture was oxidized with 3.0 mL of 3.0 M NaOH and 3.0 mL of 30% H_2O_2, stirred for four hours at room

temperature and extracted with Et_2O. The pure homoallylic alcohol was obtained upon silica gel column chromatography.

#	Aldehyde	% ee	% yield
1	C_6H_5CHO	90	91
2	*o*-BrC_6H_4CHO	89	92
3	$C_6H_{11}CHO$	85	88
4	$PhCH_2CHO$	86	89

Example 3 **Preparation of B-allyldiisopinocampheylborane.**

To a flame dried 500 mL round bottomed flask cooled under an inert atmosphere, was added B-methoxydiisopinocampheylborane (15.82 g, 50 mol) under nitrogen and dissolved in 50 mL ether and cooled to -78 °C. Allyl magnesium bromide (50 mL, 50 mmol) was added drop wise to the borinate solution and stirred for 1hour. After the completion of the reaction as monitored by ^{11}B NMR (δ 79), the reaction mixture was filtered under nitrogen using Kramer's filter and was washed repeatedly with ether. The organic layer was concentrated under vacuum in nitrogen atmosphere. Spectroscopic grade pentane was added to it using a cannula, stirred for 5 minutes and allowed to settle down. The unreacted Grignard reagent and the magnesium salts get precipitated in pentane. The supernatant liquid was then transferred via a cannula into another round bottom flask under nitrogen and the solvent was evaporated off under vacuum. After repeated washing with pentane, the concentrate (>95%, 47.5 mmol) was dissolved in 47.5 mL pentane so as to prepare a 1 M stock solution of the reagent in pentane. Similarly stock solutions were prepared in different solvents such as dioxane, benzene, etc.

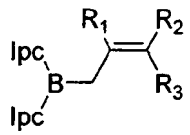
All publications, patents, and patent documents are incorporated by reference herein, as though individually incorporated by reference. The invention has been

described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

CLAIMS

What is claimed is:

1. A method comprising storing a borane of formula (I):



(I)

wherein R_1, R_2, and R_3 are each independently selected from H, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, aryl, and aryl$(C_1$-$C_6)$alkyl; and each Ipc is isopinocampheyl; under conditions such that less than 10% of the borane by weight decomposes after three days.

2. The method of claim 1 wherein the borane is B-allyldiisopino-campheylborane.

3. The method of claim 2 wherein the B-allyldiisopinocampheylborane is stored in the presence of a solvent.

4. The method of claim 3 wherein the solvent comprises a $(C_5$-$C_{12})$ hydrocarbon, a $(C_4$-$C_{10})$ ether, or a halogenated $(C_1$-$C_{10})$ hydrocarbon, or a mixture thereof.

5. The method of claim 3 wherein the solvent comprises pentane or dioxane.

6. The method of claim 3 wherein the solvent is pentane.

7. The method of claim 3 wherein the solvent is dioxane.

8. The method of claim 2 wherein less than about 5% of the B-allyldiisopinocampheylborane by weight decomposes after thirty days.

9. The method of claim 1 wherein the B-allyldiisopinocampheylborane is stored in an inert environment.

10. The method of claim 7 wherein the inert environment comprises argon or nitrogen gas.

11. The method of claim 9 wherein the B-allyldiisopinocampheylborane is stored in an air-tight vial or air-tight ampoule.

12. The method of claim 2 wherein the B-allyldiisopinocampheylborane is stored below room temperature.

13. The method of claim 2 wherein the B-allyldiisopinocampheylborane is stored at room temperature.

14. A method comprising treating a compound comprising a carbonyl group or an imine group with B-allyldiisopinocampheylborane that is at least 3 days old.

15. The method of claim 11 wherein the B-allyldiisopinocampheylborane is at least 10 days old.

16. A composition comprising dioxane and B-allyldiisopinocampheylborane.

17. The composition of claim 16 which is a solid.

18. A kit comprising 1) packaging material, and 2) B-allyldiisopino-

campheylborane that is at least 3 days old.

19. The kit of claim 18 wherein the B-allyldiisopinocampheylborane is in a solvent that comprises dioxane or pentane, or a mixture thereof.

20. A method comprising reducing an organic compound with a borane in an aqueous solvent.

21. The method of claim 20 wherein the aqueous solvent is water.

22. A method comprising reducing an organic compound with a borane at a temperature of greater than or equal to -5 °C.

23. The method of claim 22 wherein the organic compound is treated with a borane at a temperature of greater than or equal to about 10 °C.

Abstract

The invention provides methods for storing boranes (e.g. B-allyldiisopinocampheylborane). The invention also provides stable compositions comprising B-allyldiisopinocampheylborane, as well as methods for carrying out allylboration at high temperature and/or in the presence of water.